IN THE UNITED STATES PATENT AND TRADEMARK OFFICE PATENT
Re: Appeal to The Board of Patent Appeals and Interferences APPLICATION

In re PATENT APPLICATION of
Inventor(s): HETTCHE, Helmut
Appln. No.: 0 7 / 551,644
series code ↑ ↑ serial no.

Group Art Unit: 152
Examiner: L. Piccone

RECEIVED
MAY 0 8 1992
GROUP 150

Filed: November 12, 1991

Title: AZELASTINE-CONTAINING MEDICAMENTS

(Our Deposit Account No. 03-3975
(Our Order No. 326 / 62748
C# / M#
Atty. Dkt. 62748 / 87-217 PH
M# / Client Ref.

Date: April 28, 1992

#19

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231
Sir:

1. [ ] **NOTICE OF APPEAL**: Applicant hereby appeals to the Board of Patent Appeals and Interferences from the decision (not Advisory Action) dated September 12, 1991 of the Examiner twice/finally rejecting claims 1 - 18.

2. [X] **BRIEF** on appeal in this application is attached in triplicate.

3. [ ] An **ORAL HEARING** is respectfully requested under Rule 194 (due one month after Examiner's Answer or three months after filing a reply to new ground rejection in Examiner's Answer. Neither due date is extendable).

4. [ ] Reply Brief (only to new point(s) of argument, Rule 193(b)) is attached in triplicate.

5. [ ] Reply Brief (on new ground(s) of rejection, Rule 193(b)) is attached in triplicate.

6. [ ] "Small entity" verified statement filed: [ ] herewith. [ ] previously.

7. **FEE CALCULATION:**

Fees

	Large/Small Entity	
If box 1 above is X'd,	enter $260/$130*	$
If box 2 above is X'd,	enter $260/$130*	$ 260.00
If box 3 above is X'd,	enter $220/$110*	$
If box 4 or 5 above is X'd,	enter -0- (no fee)	$

8. Original due date: April 12, 1992

9. **Petition is hereby made** to extend the original due date to cover the date of this paper and any enclosure for which the requisite fee is (Large/Small Entity: 1 month $110/$55; 2 months $350/$175; 3 months $810/$405; 4 months $1,280/$640) + 110.00

10. **Subtotal** $370.00

11. Enter amount of extension fee paid [ ] previously since above original due date (item 8) [ ] with concurrently filed amendment- and subtract

12. **TOTAL FEE** $ 370.00

13. [X] Fee Attached

14. [ ] *Fee NOT required since paid in prior appeal in which the Board of Patent Appeals and Interferences did not render a decision on the merits.

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown in the heading hereof for which purpose a duplicate copy of this sheet is attached. **This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed.**

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT Application of

Helmut HETTCHE

Serial No. 07/551,664

Filed: July 12, 1992

For: AZELASTINE-CONTAINING MEDICAMENTS

Group Art Unit: 152

Examiner: L. Piccone

19/EXT D & Brief

April 28, 1992

BRIEF FOR THE APPLICANT

Dell 5/11/92

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

This is an appeal from the final rejection of claims 1-12 and 18.

STATUS OF CLAIMS

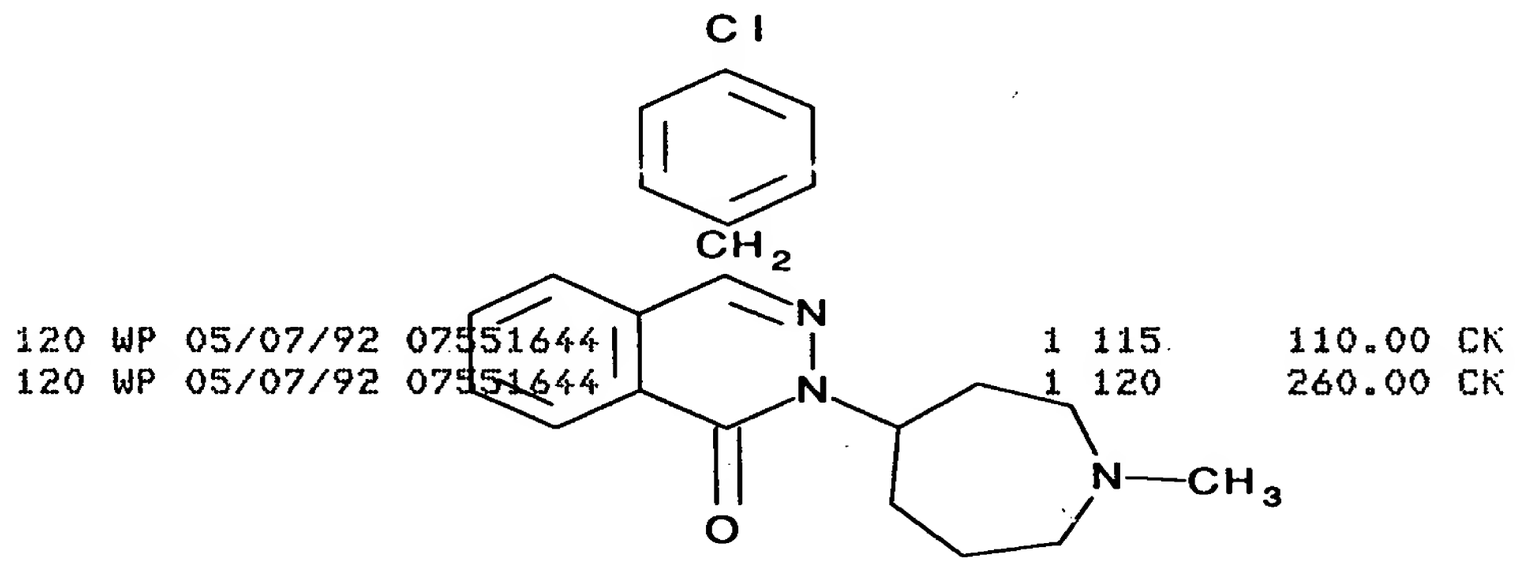
The application originally contained claims 1-18. Claims 13-17 have been cancelled, leaving claims 1-12 and 18, which are presented in this appeal.

STATUS OF AMENDMENTS

An amendment was submitted after the final rejection, cancelling claims 13-17. It has been entered.

SUMMARY OF THE INVENTION

The invention relates to a new use of azelastine, a phthalazinone derivative having the formula:



Azelastine has been used in prophylactic treatment of asthma and for its anti-allergic and antihistamine properties.

The present invention is based on a surprising discovery that azelastine and its physiologically acceptable salts display advantageous and surprising effects when applied directly in the nose and/or to the conjunctival sac of the eye. This treatment produces elimination or marked relief in allergy-related rhinitis, the common cold, and vasomotor cold. Further, application directly in the nose has been found to have advantageous effects on the mucous membrane of the eye.

The invention is claimed in claim 1 as a method which comprises *applying* azelastine *directly to the nasal tissues or to the conjunctival sac of the eye.* Claims 2-8 relate to more preferred features of the pharmaceutical composition containing azelastine which is applied in accordance with the method of claim 1. Claims 9-11 relate to more preferred modes of application of the azelastine-containing composition. Claim 12 is similar to claim 1, in defining a method of treatment with azelastine. However, it defines the symptoms which are treated more specifically than in claim 1, i.e., "a patient suffering from allergy-related or vasomotor or rhino virus-related colds or symptoms."

Claim 18 relates to a novel composition containing azelastine which is useful for the present invention. More specifically, Claim 18 relates to a powder containing azelastine and an appropriate pharmaceutical solid carrier.

ISSUES

The Examiner has rejected claims 1-12 and 18 as obvious under 35 U.S.C. § 103 over Vogelsang, U.S. Patent 3,813,384 "in view of art admitted in the specification." The Examiner separately rejected claims 13-17. However, since those claims have been cancelled, it is assumed that the

grounds of rejection applied against those claims are no longer at issue.

GROUPING OF CLAIMS

The Examiner has grouped claims 1-12 and 18 together. However, applicants believe that claims 1-12 should be considered separately from claim 18.

ARGUMENT

Claims 1-12 and 18 stand rejected as obvious from the disclosure of the cited Vogelsang, et al. patent in view of "the art admitted in the specification." The claims relate to administration of azelastine directly into nasal and eye tissues.

It is not clear what aspects of the art admitted in the specification is the basis of the examiner's reference, but the introductory passage on page 1 simply mentions to the fact that azelastine has anti-allergic and anti-histamine properties. This information does not imply a mode of administration, although, as shown below, the customary mode of administration for such medications is systemic (e.g., oral or injection). Further, as the cited Vogelsang patent refers to the fact that its compounds are used for the treatment of histamine induced disturbances (see Abstract, Column 1) and allergies (Column 6, line 72), it is not seen where the above cited passage adds anything to the disclosure of the Vogelsang patent. The Examiner has referred on page 3 of the Office Action to the use of "preseruahres" (sic) in this connection, but this comment is not understood. Therefore, it is the disclosure of the Vogelsang patent which is the focus of the following remarks.

In his discussion of this patent, on page 3 of the Final Rejection, the Examiner has referred to column 43 lines 5-15 of Vogelsang, but this comment also is not understood. There is no column 43 in this patent.

The only information in the Vogelsang patent on mode of administration is in the paragraph bridging columns 6 and 7, viz.

> The compounds according to the present invention are used as active ingredients in pharmaceutical preparations and may be administered in *usual embodiments such as tablets, dragees, capsules, suppositories, drops, ointments, creams as well as injection solutions*. They are in particular used for the treatment of the various forms of allergies. Thus, they have been used successfully in humans in the treatment of asthma bronchiale, for the treatment of various disorders of the skin and mucous membranes hay fever and rhinitis vasmotorica. In general, they are administered in such treatments in a dosage of 0.4 to 4 mg. per day and human patient. The symptoms of the above allergic diseases may be effectively reduced upon a single dose for up to 24 hours. The effectiveness of the components of the present invention in humans which is produced very rapidly and over a prolonged period of time in comparison to other antihistamines, may be particularly well shown in the reduction of the size of an artificially produced lesion by means of a histamine liberator according to L. Kerp, H. Kasimiar, P.N. Tie, Med. Welt 17 NF 2794 (1966). The compounds according to the present invention may be used as such or in combination with other active ingredients as they are usual in antihistaminic preparations.

The portion which has been shown in italics above appears to be the sole basis for the rejection, and more particularly the disclosure that the compounds "may be administered in...drops..." To this, the Examiner has added the following comment:

> It would have been obvious to administer the azelastine composition of Vogelsang directly to the nasal tissues or conjunctival sac...because these are the areas to which medicament drops are normally applied.

However, the Examiner has indulged in a leap of logic which is not supported by the reference in making this comment. The reference does not say that drops are administered to the patient. It merely says that the compounds may be administered in drops. Thus, a medicine dropper is a

well known device for measuring liquids. See for example page 1329 in the attached extract from *The United States Pharmacopoeia* which describes the use of a medicine dropper and its ability to deliver a measured quantity of liquid, with various degrees of precision. But there is no indication of where the drops are to be delivered. For example, a medicine dropper is used as a means of delivering a measured quantity of a concentrated liquid to water which is to be swallowed or used as a mouthwash.

The Examiner has cited no reference to support his contention that "the nasal tissues or conjunctival sac...are the areas to which medicament drops are normally applied." However, such a sweeping statement, which provides the sole link between the Vogelsang patent and the present invention, should be supported by a reference.

Referring again to the attached extract from *The United States Pharmacopoeia*, it will be noted that various modes of administration are discussed. Compositions which are intended to be administered to the nose are referred to as "Nasal Solutions" and compounds which are administered to the eye are referred to as "Ophthalmic Solutions", see pages 1655 and 1338. On the other hand, among the forms of medicine which are described, the word "drops" does not appear as a form of material to be administered to the eyes or nasal passages.

Similarly, the words "ointment" and "cremes" are used in the reference, and these are mentioned in the attached copy of an extract from Remington's *Pharmaceutical Sciences*. See pages 1594 and 1616. However, there is no indication of direct application to nasal passages and eyes.

Finally, there is attached a copy of an extract from *Drug Facts and Comparisons*. While numerous antihistamines are mentioned, and modes of administration are described, there is no suggestion of direct application to the eyes and

nasal passages. Dosage forms such as capsules, tablets, injections, suppositories, elixirs and syrups are described, but none for direct application to the eyes and nasal passages.

Therefore, the only link between the present invention and the cited Vogelsang reference is the Examiner's interpretation of the word "drops" in this patent, and the Examiner's unsubstantiated comment that "the nasal tissues or conjunctival sac...are the areas to which medicament drops are normally applied." However, as indicated above, such a sweeping statement, providing the sole link between the reference and the present invention and the cited patent, ought to be supported by a reference. Since none has been cited, it is submitted that the claims should be allowed.

Further, applicant requests that the Board consider the decision in the case of *Ex parte Keith*, 154 USPQ 320, which held:

> Asserted inherency must be a necessary result and not merely a possible result. Ex parte Vander Wal et al., 705 O.G. 5, 1956 USPQ 11, 109 USPQ 119, and decisions cited therein.

Here, the Examiner reasons that the only possible meaning of the reference to "drops" in the reference is that they are to be applied directly to the eyes and nasal passages. However, the Examiner has not shown, by citation of a reference, or in any other way, that this is the only possible meaning of the word "drops." Rather, a medicine dropper is simply a device for measuring a liquid. While droppers are used to administer liquid medications to eyes and nasal passages, this does not mean that this mode of administration is the "necessary" and only "possible" inference to be drawn from the reference to "drops" in the cited patent.

The foregoing comments are applicable to both claims 1-12 and claim 18. However, the following additional com-

ments are thought to be appropriate specifically to claim 18.

Claim 18 relates to a powder containing azelastine and a pharmaceutical carrier. Powders are not among the materials mentioned in the cited Vogelsang patent, and so this claim is clearly patentable.

CONCLUSION

For these reasons, it is submitted that the claims are patentable and that they should be allowed.

Respectfully submitted,
CUSHMAN, DARBY & CUSHMAN

By _____
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APPENDIX

THE CLAIMS

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/weight) azelastine.

3. A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim 1 in which the medicament is a solution.

7 A method as set forth in claim 1 in which the medicament is an aqueous solution.

8. A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1%

(weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim 1 in which the medicament is applied by spraying.

10. A method as set forth in claim 1 in which the medicament is applied as drops.

11. A method as set forth in claim 1 in which the medicament is a powder.

12. A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

18. Powder containing 0.0005 to 2% of azelastine or a physiologically acceptable salt of azelastine as active agent together with conventional pharmaceutical carrier substances.

CHECKLIST FOR BOARD APPEAL CASES

REQUIREMENTS FOR BRIEFS WHERE NOTICE OF APPEAL WAS FILED ON OR AFTER SEPTEMBER 12, 1988

SERIAL NO. 07-551644 PSE L. Bush A.U. 1503

DATE OF REVIEW 5-12-92

MISSING SECTION HEADINGS (underline defect)

☐ The brief does not contain the items required under 37 CFR 1.192(c), or the items are not under the proper heading or in the proper order.

MANDATORY ORDER OF HEADINGS

STATUS OF CLAIMS

1.A. ☐ The brief does not contain a statement of the status of all claims, pending or cancelled.

B. ☐ and does not identify the appealed claims

STATUS OF AMENDMENTS

2. ☐ The brief does not contain a statement of the status of each amendment filed subsequent to the final rejection. 37 CFR 1.192(c)(2).

SUMMARY OF INVENTION

3. ☐ The brief does not contain a concise explanation of the claimed invention, referring to the specification by page and line number and to the drawing, if any, by reference characters. 37 CFR 1.192(c)(3).

ISSUES

4. ☐ The brief does not contain a concise statement of the issues presented for review. 37 CFR 1.192(c)(4).

GROUPING OF CLAIMS (OPTIONAL)

5. ☐ Not included, examiner must use form paragraph 12.55.1.

ARGUMENT (for each issue)

6. ☐ The brief does not present an argument under a separate heading for each issue on appeal. 37 CFR 1.192(c)(6).

APPENDIX OF CLAIMS

7. ☐ The brief does not contain a correct copy of the appealed claims as an appendix thereto. 37 CFR 1.192(c)(7).

8. ☐ Explanation in support of items 1-7 above, if appropriate:

Penny,

The combined declarations are not commensurate in scope with the claims. Note "Paper No 6" refers to "Assuming a molecular weight of 400". This casts further doubt on the showing since it appears that applicant doesn't know what concentration was used. What is the basis of this assumption?

There's a PTO 1449 in file that hasn't been considered by you..

Also, there are still several 112 problems (see attached sheets) with the claims. Further, I don't see why the containers would be allowable just because they contain his ointment.

Do not allow and Maintain Finality of action at this stage.

Mel G.

Claim 1

improper Markush language

Should read: a member [of]

<u>selected from</u> the group...

Claims 2 - 4 refer to %'s of azelastine but do not indicate the applicability to the "physiologically active salts"

Claim 12, same problem as claim 1

Claim 15 "predetermined amount" is indefinite.

Claim 18 is improper and indefinite. What are "conventional pharmaceutical carrier substances"

Scope of Claim (?)

Page 5 of spec, lines 15-16

requirement for "formulations of the invention"

to contain 0.0005-2 % (weight/weight) of free

azelastine for solutions, suspensions, ointments

emulsions, creams, gels, aerosols)

This application appeals to be allowable.

The applicant has supplied two declarations (I requested a second one because the first did not provide concentration details about the two substances being compared.) The closest prior art is Engel, which discloses a benzylphthalazinone having antiallergic action. The applicant indicates that azelastine has antiallergic activity.

In his declarations the applicant describe an unexpected result; azelastine was twice as effective as the compound of Engel et al in preventing the liberation of histamine from rat mast cells.

The applicant indicates in his latest declaration that a concentration of 10 u Mo of azelastine was twice as effective in the inhibition of histamine liberation (when 0.1 ml was used to treat 10 u Mol/l of mucus) as was the same concentration of the compound of Engel et al.

P. Prater